Natural Products

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Asymmetric Total Synthesis of a Pentacyclic *Lycopodium* Alkaloid: Huperzine-Q**

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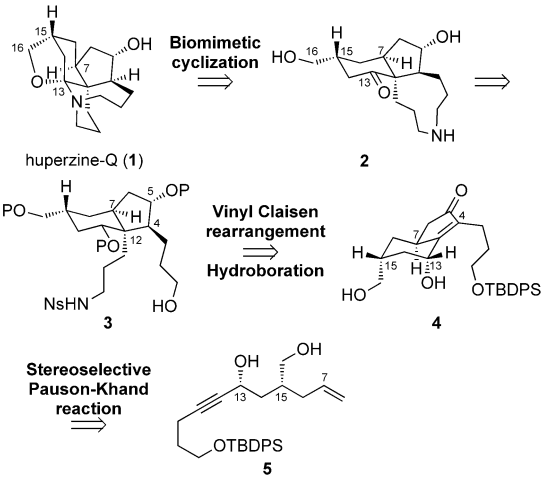
Lycopodium alkaloids have unique skeletal characteristics[1] and a variety of biological activities, such as acetylcholine esterase (AChE) inhibition[2] and neurite outgrowth promotion,[3] which have sustained the interest of many researchers of natural product chemistry, synthetic chemistry, and medicinal chemistry.

In particular, the structural diversity of fawcettimine-type *Lycopodium* alkaloids has attracted the attention of several groups as targets for total synthesis.[4]

Huperzine-Q (**1**; Figure 1), which was isolated from *Huperzia serrata* by Zhu and co-workers in 2002,[5] consists of a unique pentacyclic skeleton possessing a spiroaminal moiety and six stereogenic centers, including a quaternary carbon center. Although its structure and relative stereochemistry were determined by spectroscopic and single-crystal X-ray diffraction analysis, its absolute configuration and biological activities have not been reported thus far. To develop an efficient synthetic route to **1** and to confirm its absolute configuration, we embarked on the asymmetric total synthesis of huperzine-Q (**1**).

Our synthetic plan is shown in Scheme 1. Biogenetically, **1** would be derived from the fawcettimine derivative **2** by intramolecular spiroaminal formation between a primary alcohol at C16 and a secondary amine. We anticipated an efficient synthesis of **2** to arise from azonane ring formation by utilizing the intramolecular Mitsunobu reaction and subsequent functional group transformations of **3**, which could be a key intermediate to several fawcettimine-type *Lycopodium* alkaloids such as lycoposerramine-A[6] (Figure 1). We envisioned that successive chiral centers (C5, C4, and C12) in **3** could be constructed from the bicyclic cyclopentenone **4** by means of a vinyl Claisen rearrangement, and the subsequent hydroboration/oxidation process. Bicyclic compound **4** was expected to be elaborated from the chiral diol **5** through the novel stereoselective Pauson–Khand reaction (PKR; Scheme 1).



Scheme 1. Retrosynthetic analysis of huperzine-Q (**1**). Ns = 2-nitrobenzenesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

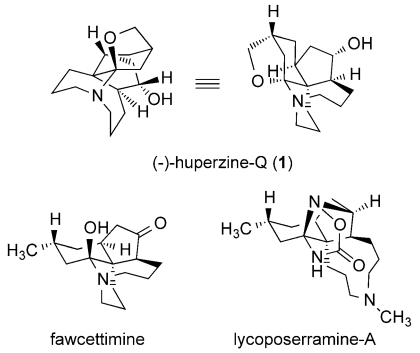


Figure 1. Structures of huperzine-Q (**1**), fawcettimine, and lycoposerramine-A.

Our synthesis commenced with the coupling between the acyl chloride **6** and alkyne **7** to afford ketone **8**,[7] which was transformed into the optically active lactone **9** in a one-pot operation involving the Noyori reduction[8] and successive treatment with PPTS. The enantiomeric excess was determined to be 83% by HPLC analysis using a chiral stationary phase[9] (the enantiomeric excess of the product was finally raised to 99% *ee* during conversion into **15**. See below). Then, an allyl unit was introduced to the α position of the carbonyl group in **9** to furnish **10** and **11** in quantitative yields in a ratio of 2.3:1.[10] The conversion of **10** into **11**, having the desired stereochemistry at C15, was successfully achieved by treatment with LHMDS and subsequent addition of a hindered acid (BHT), thus giving the kinetically controlled product **11** with excellent selectivity (**10**/**11** = 1:16.5). The reduction of lactone **11** afforded diol **5** for the PKR (Scheme 2).

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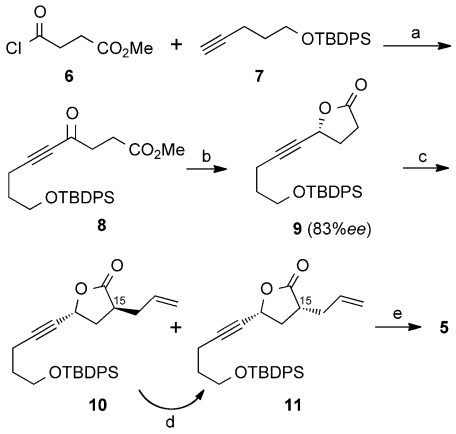
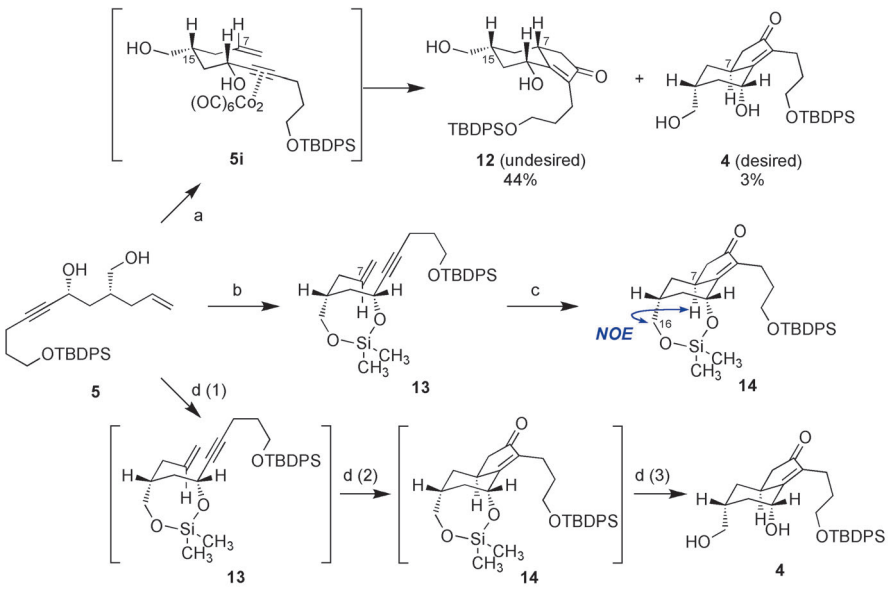
Initial attempts to perform the PKR with **5** gave, however, **12**, the undesired C7 epimer as the major product. Mechanistic considerations indicated that a reaction intermediate such as **5i** would have a chairlike conformation with an equatorial side chain at C15, and therefore control the stereochemistry at C7. On this basis, we devised the silyl-tethered compound **13**, which would alter the conformation of the reaction intermediate to yield a bicyclic product having the desired C7 stereochemistry. Actually, the silyl-tethered compound **13** gave the desired compound **14** in 57% yield under conventional PKR conditions.[11] NOE experiments showed that C7 in **14** had the desired stereochemistry (Scheme 3). Next, we optimized the reaction conditions to develop the one-pot operation to transform **5** into **4**. First, we prepared the silyl-tethered compound **13**, to which $[Co_2(CO)_8]$ was added, thus affording the alkyne cobalt complex of **13**. Then, we diluted the reaction mixture with toluene and heated it under CO atmosphere to give the bicyclic compound **14**, which in turn was directly treated with concentrated hydrochloric acid in MeOH to give the desilylated compound **4** in 92% yield from **5**. To the best of our knowledge, this is a first example of a stereoselective PKR that utilizes a seven-membered silyl-tethered compound.



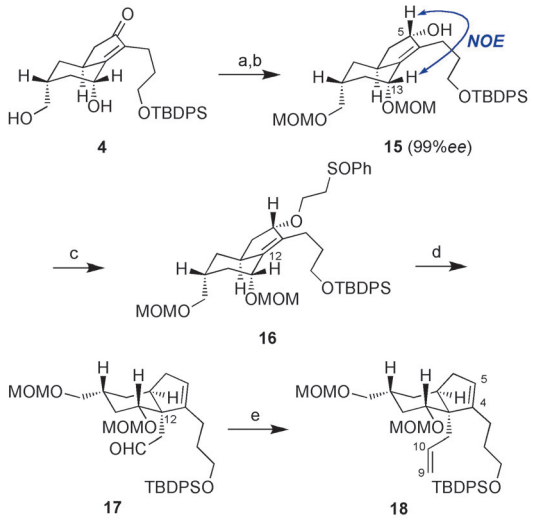
Scheme 2. Synthesis of the chiral diol **5**. Reagents and conditions: a) *n*BuLi, $ZnCl_2$, THF, −78 °C, 91%; b) [Ru{(*R*,*R*)-Tsdpen}(*p*-cymene)], *i*PrOH, 28 °C and then PPTS, toluene, 80 °C, 68%; c) Allylbromide, LHMDS, HMPA, THF, −78 °C, quant, **10**/**11** = 2.3:1; d) LHMDS, THF, −78 °C and then BHT, 86%, **10**/**11** = 1:16.5; e) $LiBH_4$, THF, RT, 95%. BHT = 2,6-di-*t*butylated-hydroxytoluene, dpen = 1,2-diphenylethylenediamine, HMPA = hexamethylphosphoramide, LHMDS = lithium bis(trimethylsilyl)amide, PPTS = pyridinium *p*-toluenesulfonate, THF = tetrahydrofuran.

Our next task was the construction of the azonane ring using the intramolecular Mitsunobu reaction (Scheme 5). We prepared substrate **19** for the Mitsunobu reaction from diene **18** by using a sequential reaction that involved a simultaneous hydroboration/oxidation[15] at two positions (C4–C5 and C9–C10), the introduction of a nitrogen functional group to C9, and the subsequent removal of a TBDPS group. With the Ns-protected derivative **19** in hand, we tried to construct the azonane ring. After several screening steps, we found that the treatment of **19** with diethyl azodicarboxylate (DEAD) in the presence of PPh_3 in toluene at 70 °C afforded **20** in excellent yield.[4e,16] At this stage, the X-ray crystallographic analysis of **20** was performed, and enabled us to confirm the absolute configuration of all the chiral centers.[17]

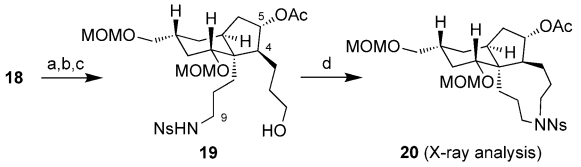


Scheme 3. Stereoselective synthesis of bicyclic compounds **12** or **14** and one-pot operation to give **4**. Reagents and conditions: a) $[Co_2(CO)_8]$ toluene, RT to 100 °C under CO atmosphere, 44% of **12** and 3% of **4**; b) $SiMe_2Cl_2$, Et_3N, DMAP, CH_2Cl_2, RT, 85%; c) $[Co_2(CO)_8]$, toluene, RT to 100 °C under CO atmosphere, 57%; d) 1. $SiMe_2Cl_2$, Et_3N, DMAP, $(CH_2Cl)_2$, RT, 2. $[Co_2(CO)_8]$, toluene, RT to 100 °C under CO atmosphere, 3. HCl, MeOH, 0 °C, 92%. DMAP = *N*,*N*-4-dimethylaminopyridine.

For the completion of the total synthesis of **1**, we converted **20** into the fawcettimine derivative **2** as follows (Scheme 6). The removal of the two MOM groups with trimethylsilyl bromide gave the corresponding diol **21** in quantitative yield.[18] Then, the selective acetylation of the primary alcohol[19] at C16 and the subsequent Dess–Martin oxidation of the secondary alcohol at C13 were carried out in a one-pot operation to afford **22**. The successive removal of the Ns group and diacetyl groups was also



Scheme 4. Synthesis of the diene **18**. Reagents and conditions: a) MOMCl, DIPEA, TBAI, CH_2Cl_2, RT, 84%; b) (*R*)-Me-CBS, BH_3·THF, THF, RT, 88% (d.r. 9.8:1); c) Phenylvinylsulfoxide, KH, NaH, THF, RT, 98%; d) $NaHCO_3$, 1,2-dichlorobenzene, 170°C, 89%; e) *n*BuLi, PPh_3CH_3Br, THF, RT, 95%. (*R*)-Me-CBS = (*R*)-methyloxazaborolidine, DIPEA = diisopropylethylamine, MOM = methoxymethyl, TBAI = tetra-*n*-butylammonium iodide.

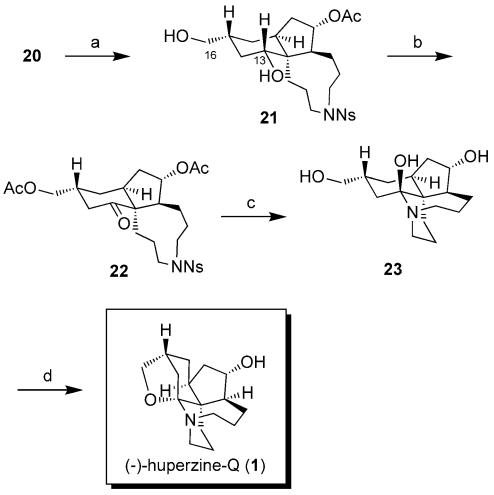


Scheme 5. Synthesis of the azonane compound **20**. Reagents and conditions: a) BH_3·SMe_2, THF, 0°C; BH_3·THF, 0°C; then $NaBO_3$·4 H_2O, RT, 67%; b) 1. MsCl, Et_3N, CH_2Cl_2, 0°C then Ac_2O, DMAP, pyridine; 2. NH_2Ns, K_2CO_3, DMF, 80°C, 97%; c) TBAF, AcOH, THF, RT, quant; d) DEAD, PPh_3, toluene, 70°C, 94%. DEAD = diethyl azodicarboxylate, DMF = *N*,*N*-dimethylformamide, Ms = methanesulfonyl, Ns = 2-nitrobenzenesulfonyl, TBAF = tetra-*n*-butylammonium fluoride.

achieved in a one-pot operation to give a product that was proven to exist as carbinolamine form **23** by analysis of NMR spectra.

Then, we attempted to convert **23** into the spiroaminal form **1** based on a biogenetic hypothesis. After considerable efforts, we found that this spiroaminal formation occurred by treating of **23** with anhydrous (+)-camphorsulfonic acid in refluxing toluene to furnish (−)-huperzine-Q (**1**) in 86% yield. By direct comparison with natural huperzine-Q, which was isolated from *Lycopodium serratum* in our laboratory, we found that synthetic **1** was completely identical in all respects with the natural product, including the optical properties.[20] Hence, the structure including the absolute configuration was confirmed.

In summary, the first asymmetric total synthesis of (−)-huperzine-Q (**1**) has been achieved in 19 steps and 16.4% overall yield starting from methyl-4-chloro-4-oxobutylate (**8**). The synthesis involved a novel stereoselective PKR utilizing a



Scheme 6. Completion of total synthesis of (−)-huperzine-Q (**1**). Reagents and conditions: a) TMSBr, CH_2Cl_2, 0°C, quant; b) AcCl, 2,6-lutidine, CH_2Cl_2, −78°C and then Dess–Martin periodinane, RT, 96%; c) PhSH, K_2CO_3, MeCN, 30°C and then MeOH, K_2CO_3, 30°C, 98%; d) CSA, toluene, reflux, 86%. CSA = (+)-camphorsulfonic acid, TMS = trimethylsilyl.

silyl-tethered substrate, the construction of a quaternary carbon center through a vinyl Claisen rearrangement, and a biomimetic spiroaminal formation. This strategy is an effective approach to use towards other fawcettimine-type *Lycopodium* alkaloids.

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